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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,591	KONDOW ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 23-25* is/are pending in the application.

4a) Of the above claim(s) *9 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8 and 10* is/are rejected.

7)☒ Claim(s) *2 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/01 and 5/02*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of species nucleotide sequencing in the presence of an immobilized nucleic acid template and a primer solution (claims 1-11) and species DNA polymerase and dNTP (claims 1-8, 10, and 11) is acknowledged. The traversal is on the ground(s) that "the office has failed to meet thc burden necessary in order to sustain the Restriction Requirement." of Groups I and III since "the Office has not provide reasons or examples to support a conclusion that the species are indeed patentably distinct."; (2) "a search of all claims would not impose a serious burden on the Office."; and (3) "should the elected species be found allowable, the Office should expand its search to the non-elected species.".

After carefully considered applicant's arguments, the examiner agreed to withdraw species election for nucleotide sequencing in the presence of an immobilized nucleic acid template and a primer solution (claims 1-11) and nucleotide sequencing in the presence of an immobilized primer and a nucleic acid template solution (claims 1-11). However, the above arguments have not been found persuasive toward the withdrawal of species election for DNA polymerase and dNTP (claims 1-8, 10, and 11) and RNA polymerase and NTP (claims 1-7 and 9-11) such that all species will be examined together. First, the examiner agrees with applicant that "should the elected species be found allowable, the Office should expand its search to the non-elected species.". Second, according to MPEP 809.02, "[S]hould applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the

case. ". However, in response to the restriction requirement mailed on November 18, 2002, applicant does not provide any evidence to show that species of DNA polymerase and dNTP and species of RNA polymerase and NTP are not patentably distinct. Third, although, in previous office action, the examiner did not provide examples to support a conclusion that species of DNA polymerase and dNTP and species of RNA polymerase and NTP were indeed patentable distinct, it would have been obvious to one having ordinary skill in the art to know that DNA polymerase (for DNA synthesis) and RNA polymerase (for RNA synthesis) have different structures and different functions, which requires different searches. Although both species of DNA polymerase and dNTP and species of RNA polymerase and NTP require to search nucleic acid sequencing, their searches do not overlap because these species are directed to different methods that require different polymerases and different nucleotide triphosphates to perform method steps.

Therefore, the requirement is still deemed proper and is therefore made FINAL.

Sequence Rules Compliance

2. The original filed sequencing listing has complied with Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim Objections

3. Claim 1 is objected to because of the following informalities: (1) since it appears that "a nucleic acid molecule" in steps (a) and (b) are different, the examiner suggests applicant to change "a nucleic acid molecule" in steps (a) and (b) as first and second nucleic acid molecules; and (2)

since, from the claim, it appears that the nucleotide reacted with the 3' end of said primer and a nucleotide which forms a base-pair with a base are an identical nucleotide, the phrase "allowing the nucleotide to react with the 3' end of said primer, whereby a nucleotide, which forms a base-pair with a base" in step (c) should be "allowing the nucleotide to react with the 3' end of said primer, whereby the nucleotide, which forms a base-pair with a base"; (3) the phrase "DNA polymerase" in step (c) should be " a DNA polymerase" and the phrase "RNA polymerase" in step (c) should be "a RNA polymerase".

4. Claim 10 is objected to because of the following informality: in order to keep consistence between step (d) of claim 1 and claim 9, the examiner suggests applicant to change "said dNTP and NTP" to "said dNTP or NTP".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-8, 10, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 2-8, 10, and 11 are dependent on claim 1.

7. Claim 1 is rejected as vague and indefinite in view of "single dye molecule" because it is unclear that "single dye molecule" means one type of dye molecule or "single dye molecule" means only one dye molecule. Please clarify.

8. Claim 1 is rejected as vague and indefinite in view of steps (a) and (b) of the claim because it is unclear that " a primer" in step (a) and (b) are the same or different. If "a primer" in step (a) and (b) are the same, "a primer" in step (b) should be "the primer". Please clarify.

9. Claim 1 is rejected as vague and indefinite in view of the phrase "allowing the nucleotide to react with the 3' end of said primer, whereby a nucleotide, which forms a base-pair with a base opposed to the reaction site" in step (c) because it is unclear what it intended. From the claim, it appears that "a base opposed to the reaction site" is paired with a nucleotide locates on the immobilized nucleic acid, applicant is suggested to amend the claim to specify that the base is paired with a nucleotide locates on the immobilized nucleic acid. Furthermore, there is insufficient antecedent basis for the limitation "the reaction site" in the claim because there is no "a reaction site" in steps (a), (b) and (c). Please clarify.

10. Claim 4 recites the limitation "the thus released fluorescent signal" in the claim. There is insufficient antecedent basis for this limitation in the claim because there is no "released fluorescent signal" in step (d) of the claim. Please clarify.

11. Claim 6 recites the limitation "said disruption of dye molecules in (e) is performed by irradiation of a laser beam stronger than in (d)" in the claim . There is insufficient antecedent basis for this limitation in the claim because there is no "laser beam" in step (d). Please clarify.

12. Claim 10 is rejected as vague and indefinite in view of the phrase "dNTP and NTP" because claims 1 and 10 do not correspond each other since step (c) of claim 1 only requires either dNTP or NTP and does not require both dNTP and NTP. Therefore, claim 10 lacks sufficient antecedent basis for the phrase "dNTP and NTP". Please clarify.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

14. Claims 1, 3, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheeseman (US Patent No. 5,302,509, published on April 12, 1994).

The claimed invention is drawn to a method for determining a nucleotide sequence of a nucleic acid. Claim 1 requires following method steps: (a) immobilizing a nucleic acid molecule, or a primer which has a sequence complementary to a part of the sequence of the nucleic acid molecule, onto the surface of a solid; (b) annealing the primer, which has a sequence complementary to a part of the sequence of the nucleic acid molecule, or anneal the nucleic acid molecule to the primer; (c) providing a solution which contains a DNA polymerase and one type of dye-labeled dNTP or a RNA polymerase and one type of dye-labeled NTP to said immobilized nucleic acid molecule, and allowing the nucleotide to react with the 3' end of said primer whereby the nucleotide forms a base-pair with a base of the nucleic acid molecule and is bound to the primer by action of the polymerase; (d) detecting a bound, dye-labeled dNTP or NTP; (e)

disrupting the dye molecule of the bound, dye-labeled dNTP or NTP; (f) repeating (c) to (e) while changing the type of dye-labeled dNTP or NTP in turn, to sequentially bind dNTPS or NTPS which forms a base-pair with the nucleotides of the nucleic acid molecule; and (g) determining a nucleotide sequence of the nucleic acid molecule based on the types of the sequentially bound dNTPs or NTPs. Claim 3 requires to optically detect the dye molecule of the dye-labeled dNTP. Claim 7 requires that the dye is a fluorescence dye.

Cheeseman teaches method for sequencing polynucleotides. This method comprised following steps: (a) providing a set of identical single strand DNA molecules (ssDNA) comprising at the 3' end a leader sequence, the leader sequence comprising a region recognizable by a DNA polymerase for initiation of replication; (b) providing an oligonucleotide complementary to at least a portion of the leader sequence, and capable of forming a stable double stranded DNA hybrid therewith; (c) covalently attaching the 3' end of the leader sequence, the 5' end of the ssDNA or an end of the oligonucleotide to a solid support; (d) forming a stable double strand DNA hybrid bound to the solid support, the hybrid comprising the oligonucleotide and the single stranded DNA molecule with the leader sequence and the bound hybrid acting as a primer for DNA polymerase replication; (e) exposing the hybrid bound to the solid support to a DNA polymerase in the presence of fluorescently-labeled 3'-blocked derivatives of the four nucleotide 5'-triphosphates of 2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxycytidine and 2'-deoxythymidine, where each of the four nucleotide 5'-triphosphate (NTPs) derivatives was labeled with a fluorescent label distinguishable by fluorescent detection means from the other three labels on the other three nucleotide 5'-triphosphate derivatives, under conditions whereby

the polymerase would add the appropriate complementary nucleotide 5'-triphosphate derivative to the oligonucleotide; (f) separating any unused NTP derivatives from the solid supported DNA hybrid and the support; (g) identifying the labeled NTP derivative added to the double stranded DNA by optical detection means; thereby identifying its complementary deoxynucleotide present in the single stranded DNA molecule; (h) removing the fluorescent label and 3' blocking group from the labeled NTP derivative of step (g) to expose the normal OH group in the 3'-position; (i) separating the freed blocking group and label (which might be associated with the blocking group) from the solid supported double stranded DNA hybrid; and (j) repeating steps (e) through (i) through a plurality of cycles until labeled NTPs could no longer be added to the oligonucleotide; whereby the result of each cycle identified the next deoxynucleotide in sequence in the single stranded DNA molecule (see columns 2 and 8).

Regarding claims 1, 3 and 7, since the steps (a) to (d) of Cheessman's method discloses to anneal the immobilized nucleic acid molecule (i.e., ssDNA) to the primer (i.e., an oligonucleotide complementary to at least a portion of the leader sequence of the nucleic acid molecule) or anneal the immobilized primer (i.e., an oligonucleotide complementary to at least a portion of the leader sequence of the nucleic acid molecule) to the nucleic acid molecule (i.e., ssDNA) wherein the nucleic acid or the primer is immobilized on the surface of a solid (i.e., a solid support), steps (a) and (b) of claim 1 are anticipated by Cheessman. The step (e) of Cheessman's method discloses to expose the hybridization complex between the nucleic acid molecule and the primer to a DNA polymerase in the presence of fluorescently-labeled 3'-blocked derivatives of the four nucleotide 5'-triphosphates of 2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxycytidine and

2'-deoxythymidine, where each of the four nucleotide 5'-triphosphate (NTPs) derivatives is labeled with a fluorescent label distinguishable by fluorescent detection means from the other three labels on the other three nucleotide 5'-triphosphate derivatives **(NTPs used in Cheessman's method are dNTPs because NTPs taught by Cheessman contain 2'-deoxyadenosine or 2'-deoxyguanosine, 2'-deoxycytidine or 2'-deoxythymidine)**. Although step (c) of claim 1 requires one type of dye-labeled dNTP while step (e) of Cheessman's method discloses to use four different kind of fluorescence dye-labeled dNTP, since the method of claim 1 is a "comprising" claim and step (c) of the claim does not limit to only one type of dye-labeled dNTP, steps (c) of claim 1 and claim 7 are anticipated by Cheessman. Since steps (g) and (h) of Cheessman's method discloses to detect a bound, dye-labeled dNTP by optical detection means and disrupt bound, dye-labeled dNTP (i.e., removing the fluorescent label and 3' blocking group), steps (d) and (e) of claim 1 and claim 3 are anticipated by Cheessman. Since step (j) of Cheeseman's method discloses to repeat steps (c) to (e) of the claim 1 by changing the type of dye-labeled dNTP in turn (i.e., repeating a plurality of cycles until labeled dNTPs can no longer be added to the oligonucleotide) and determine a nucleotide sequence of the nucleic acid molecule based on the types of the sequentially bound dNTPs (i.e., the result of each cycle identifies the next deoxynucleotide in sequence in the single stranded DNA molecule), steps (f) and (g) of claim 1 are anticipated by Cheessman.

Therefore, Cheessman teaches all limitations recited in claims 1, 3, and 7.

15. Claims 1, 3, 4, 7, and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Anazawa *et al.,* (US Patent No. 6,136,543, 102(e) date: July 30, 1999).

The claimed invention is drawn to a method for determining a nucleotide sequence of a nucleic acid. Claim 1 requires following method steps: (a) immobilizing a nucleic acid molecule, or a primer which has a sequence complementary to a part of the sequence of the nucleic acid molecule, onto the surface of a solid; (b) annealing the primer, which has a sequence complementary to a part of the sequence of the nucleic acid molecule, or anneal the nucleic acid molecule to the primer; (c) providing a solution which contains a DNA polymerase and one type of dye-labeled dNTP or a RNA polymerase and one type of dye-labeled NTP to said immobilized nucleic acid molecule, and allowing the nucleotide to react with the 3' end of said primer whereby the nucleotide forms a base-pair with a base of the nucleic acid molecule and is bound to the primer by action of the polymerase; (d) detecting a bound, dye-labeled dNTP or NTP; (e) disrupting the dye molecule of the bound, dye-labeled dNTP or NTP; (f) repeating (c) to (e) while changing the type of dye-labeled dNTP or NTP in turn, to sequentially bind dNTPS or NTPS which forms a base-pair with the nucleotides of the nucleic acid molecule; and (g) determining a nucleotide sequence of the nucleic acid molecule based on the types of the sequentially bound dNTPs or NTPs. Claim 3 requires to optically detect the dye molecule of the dye-labeled dNTP. Claim 4 requires to excite dye molecules by irradiation of a laser beam and detect fluorescence signal from the dye. Claim 7 requires that the dye is a fluorescence dye. Claim 8 requires that the dye-labeled dNTP is labeled with rhodamine, tetramethyl rhodamine (fluorescein), Rhodamine 6G, fluorescein isothiocyanate, or 4-fluoro-7-nitro-benzofurazon (Texas red).

Anazawa *et al.*, teach method for determining nucleic acids base sequence and apparatus therefor. The method comprised the following steps: (a) hybridizing a primer with a template DNA wherein the template DNA was a single-stranded DNA having a bead at one end and a magnetic bead at the other end and the template DNA was fixed in the field of view of a fluorescent microscope by using a magnetic force and a laser trap (see abstract); (b) performing a complementary strand extension reaction using a polymerase for extending said hybridized primer or an extended primer produced by repeating said step (b) to following step (d), by incorporating a single caged nucleotide of four kinds of caged nucleotides to 3'-terminus of said hybridized primer or said extended primer, in the presence of said four kinds of caged nucleotides, wherein said single caged nucleotide was complementary with a base sequence of said template DNA, and each of four kinds of caged nucleotides had at least one fluorophore label, and a continuous progress of said complementary strand extension reaction was prevented after incorporating said single caged nucleotide to 3'-terminus of said hybridized primer or said extended primer; (c) exciting said fluorophore label(s) included in said single caged nucleotide incorporated to 3'-terminus of said hybridized primer or said extended primer, by laser irradiation to emit fluorescence from said fluorophore label(s), and detecting fluorescence to determine a kind of a base of said caged nucleotide incorporated to 3'-terminus of said hybridized primer or said extended primer, and determining a kind of a base of said single caged nucleotide incorporated to 3'-terminus of said hybridized primer or said extended primer; (d) releasing said fluorophore label(s) from said caged nucleotide incorporated to 3'-terminus of said hybridized primer or said extended primer, in order to bring about a state at which said complementary strand extension

reaction for extending said hybridized primer or said extended primer could proceed; and (e) repeating said step (b) to said step (d), and determining said base sequence of said template DNA one base by one base sequentially based on the kinds of bases of said caged nucleotides incorporated to said extended primer by said complementary strand extension reaction (see claims 8 and 12 in columns 22-26).

Regarding claims 1, 3, 4, and 7, the steps (a) to (d) of the method of Anazawa *et al.*, discloses to anneal the immobilized nucleic acid molecule (i.e., a single-stranded DNA template) to the primer wherein the nucleic acid is immobilized on the surface of a solid (i.e., a bead), allow a fluorescence labeled nucleotide (i.e., four kinds of caged nucleotides such as caged dATP, caged dGTP, caged dCTP, and caged dTTP, see column 6, lines 27-52) to react with the 3' of said primer in the presence of a polymerase, excite the dye molecules (i.e., fluorophore labels) on the nucleotide incorporated to 3'-terminus of said hybridized primer by irradiation of a laser beam (i.e., laser irradiation) as recited in claim 4, detect a bound, dye-labeled dNTP (i.e., detecting fluorescence to determine a kind of a base of said caged nucleotide incorporated to 3'-terminus of said hybridized primer or said extended primer) wherein the dye molecule of said dye-labeled dNTP is optically detected (i.e., measuring the single fluorophore incorporated as a fluorescence-microscopic image by evanescent irradiation with exciting laser beams, see abstract) as recited in claim 3, disrupt the dye molecule of the bound, dye-labeled dNTP (i.e., releasing of the fluorescence-labeled case dNTP by a photochemical reaction caused by ultraviolet irradiation, see column 6, lines 27-52), and repeat steps (c) to (e) of the claim 1 by changing the type of dye-labeled dNTP in turn and determine a nucleotide sequence of the nucleic acid molecule based on

the types of the sequentially bound dNTPs (i.e., repeating said step (b) to said step (d), and determining said base sequence of said template DNA one base by one base sequentially based on the kinds of bases of said caged nucleotides incorporated to said extended primer by said complementary strand extension reaction, see claim 8, step (e)). Although step (c) of claim 1 requires one type of dye-labeled dNTP while step (b) of the method of Anazawa *et al.,* discloses to use four different kind of fluorescence dye-labclcd dNTP, since the method of claim 1 is a "comprising" claim and step (c) of thc claim does not limit to only one type of dye-labeled dNTP, steps (c) of claim 1 and claim 7 are anticipated by Anazawa *et al.*. Although the method of Anazawa *et al.,* does not specify polymerase type, it is known that a DNA polymerase reaction must use a DNA polymerase (for example, see column 2, lines 16-53). For above reasons, claim 1, 3, 4, and 7 are anticipated by Anazawa *et al.*.

Regarding claim 8, Figures 31-34 showed a caged dATP, caged dCTP, caged dGTP, and caged dTTP labeled with fluorescence dyes FAM, JOE, TAMRA, and ROX (see column 19, first paragraph). Since it is known that 5-FAM, 6-JOE, 5-TAMRA, and 5-ROX are abbreviations of 5-carboxyfluorescein, 6-carboxy-4',5'-dichloro-2', 7'-dimethoxyfluorescein, 5-carboxytetramethylrhodamine, and 5-carboxy-X-rhodamine respectively, claim 8 is anticipated by Anazawa *et al.*.

Therefore, Anazawa *et al.,* teach all limitations recited in claims 1, 3, 4, 7, and 8.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anazawa *et al.,* (July 30, 1999) as applied to claims 1, 3, 4, 7, and 8 above, and further in view of Mathies *et al.,* (US Patent No.5,091,652, published on February 25, 1992).

The teachings of Anazawa *et al.,* have been summarized previously, *supra.*

Anazawa *et al.,* do not disclose to detect fluorescence signals using a confocal fluorescence microscope system as recited in claim 5. However, in their method, fluorescence signal was detected using an inverted phase-contrast and incident-light fluorescence microscope system (see column 11, lines 28-43).

Mathies *et al.,* teach to detect fluorescence signals using a confocal fluorescence microscope system (i.e., a laser excited confocal microscope fluorescence scanner) (see abstract and Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the detection recited in claim 1 using a confocal fluorescence microscopc system in view of the patents of Anazawa *et al.,* and Mathies *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Anazawa *et al.,* because Mathies *et al..,* have successfully used a confocal fluorescence microscope system to detect fluorescence signals and the simple replacement of one well known fluorescence detection device (i.e., an inverted phase-contrast and incident-light fluorescence microscope system taught by Anazawa *et al.,*) from another well known fluorescence detection device (i.e., a confocal fluorescence microscope system taught by Mathies *et al..,*) during the process of detecting fluorescence signals would have been, in the absence of convincing evidence to thc contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

18. Claims 2 and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. No claim is allowed.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
March 20, 2003